REMARKS

Claims 1 and 12 are pending. Claim 1 is amended to incorporate the limitations of Claim 2, which is cancelled. As Claim 2 is cancelled, Claim 12 is amended to depend only from Claim 1. Claims 3-11 were previously cancelled. Support for the claim amendments may be found throughout the specification. See, for example, page 6, lines 18-21. Therefore, no new matter is added.

As this Amendment is merely to incorporate the limitations of an existing dependent claim, entry of this Amendment does not raise any new issues and does not require the Examiner to conduct a new search. Applicants respectfully request entry of this Amendment under 37 CFR Section 1.116 in that it places the Claims in better form for allowance or for consideration on appeal.

Applicants thank the Examiner for acknowledging that they have perfected their claim for benefit of foreign priority under 35 USC Section 119(a)-(d). Applicants also thank the Examiner for the withdrawal of the objections to Claim 9 and the rejections of Claims 1-3 and 9 under 35 USC Section 112, second paragraph, and of Claims 1, 3, and 9 under 35 USC Section 102(b) over Vaddi et al (WO 00/23614).

Claims 1, 2, and 12 were rejected under 35 USC Section 103(a) as unpatentable over Vaddi in view of Mellgren (J. Biol. Chem. 272(47), 29899-29903, 1997). Claim 2 is cancelled and Applicants respectfully traverse with respect to Claims 1 and 12.

According to the Examiner, Vaddi "disclose a method for measuring the efficacy of drugs by measuring their ability to serve as 20S proteosome inhibitors *in vivo* (see abstract)." Whether that is true or not, Vaddi does not disclose a method for identifying a fungicide comprising: (a) contacting a candidate compound with fungal 20S proteasomes in the presence of a substrate of the fungal 20S proteasomes and in the presence of from 2 to 10% (v/v) dimethyl sulphoxide, (b) selecting those candidate compounds which specifically inhibit an enzymatic conversion of the substrate by the fungal 20S proteasomes, and (c) testing for the fungicidal action of those candidate compounds on fungi in an *in vivo* assay.

Vaddi monitors the pharmacodynamic drug action of a proteosome inhibitor by first administering the proteosome inhibitor to an animal. Vaddi then obtains a biological sample from the animal and then test the sample in an *ex vivo* assay of proteosome activity. Vaddi does not contact a candidate compound with fungal 20S

proteasomes in the presence of a substrate of the fungal 20S proteasomes *and in the presence of from 2 to 10% (v/v) dimethyl sulphoxide.* The only way this is possible by using the process of Vaddi is if the animal itself contains from 2 to 10% (v/v) dimethyl sulphoxide at the site where the candidate compound is contacted with fungal 20S proteasomes in the presence of a substrate of the fungal 20S proteasomes! Moreover, Vaddi then tests the sample in an *ex vivo* assay of proteosome activity – not an *in vivo* assay on fungi as claimed.

The Examiner blithely states that because of one word in Vaddi, namely "sepsis", that "Vaddi necessarily discloses a method for identifying effective fungicides (mycotics)." This reasoning is incorrect for a number of reasons not the least of which is that sepsis is not only caused by fungi, it can be caused by bacteria (much more common), viruses, other parasites, etc. Indeed, sepsis is predominantly caused by gram-negative bacteria such as *Escherichia coli* and other enterobacteria. Sepsis is much less frequently caused by gram-positive bacteria such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, and other streptococci. Only in very rare instances is sepsis caused by fungi, viruses, or other parasites. In other words, to contend that treating sepsis necessarily equals a method for identifying effective fungicides is absolutely wrong.

In addition, the Examiner still has not found anything in Vaddi that discloses testing for the fungicidal action of the candidate compounds on fungi in an *in vivo* assay. Surely, the Examiner cannot be contending that treating sepsis, even one that happens to be caused by fungi, is an *in vivo* assay! Even if the Examiner were to so contend, Vaddi teaches away from an *in vivo* assay because they specifically mention that "(t)he present inventors have surprisingly discovered than *ex vivo* assay of proteosome activity ... " (page 3, lines 18-19).

Mellgren cures none of the deficiencies in Vaddi. Furthermore, even Mellgren teaches away from the claimed method. Mellgren clearly states in the abstract that the peptidyl inhibitors used in the experiments had no detectable effect on the growth rates of overnight *Saccharomyces cerevisiae* cultures, even in concentrations as high as 200 μM. Therefore the Examiner's assertion on page 4 of the Office Action that such statement indicates "that the efficacy of the given protease inhibitor may be proteosome specific" is not at all supported by Mellgren. Indeed, there is no hint of such a suggestion in Mellgren.

Thus, neither from Vaddi, nor from Mellgren, can one of ordinary skill in the art conclude that potential fungicides be identified by screening for inhibitors of fungal 20S proteasomes. Moreover, even if one of ordinary skill in the art combined the teachings of Vaddi with Mellgren, the result would not be the method claimed in Claims 1 and 12. Therefore, Applicants respectfully request withdrawal of this rejection.

Claims 1 and 12 were rejected under 35 U.S.C. Section 103(a) as unpatentable over Vaddi. Applicants respectfully traverse.

Applicants have discussed the numerous deficiencies of Vaddi above. The Examiner argues that just because Vaddi discloses that any assay is suitable for evaluating proteosome activity, Vaddi necessarily teaches high throughput screening assays. The Examiner is incorrect. The high-throughput screening method involves testing the effect of a large number of different substances on cells. Once certain substances are discovered, conventional screening assay methods are employed. Vaddi monitors the pharmacodynamic drug action of a proteosome inhibitor by first administering the proteosome inhibitor to an animal. One of ordinary skill in the art would not administering proteosome inhibitors to an animal using high throughput screening assays. Therefore, Applicants respectfully request withdrawal of this rejection.

It is believed that the claims are in condition for allowance. Review and reconsideration and allowance of the claims are respectfully requested.

Respectfully submitted,

By _____
Raymond J. Harmuth
Attorney for Applicant(s)
Reg. No. 33,896

Bayer CropScience LP
2 T.W. Alexander Drive
Research Triangle Park, NC 27709
Ph: (919) 549-2102
Fax: (919) 549-3994
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